(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 972 513 A1

# (12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:
**19.01.2000 Bulletin 2000/03**

(21) Application number: **98947774.0**

(22) Date of filing: **07.10.1998**

(51) Int. Cl.[7]: **A61K 9/20**, A61K 47/36, A61K 47/46

(86) International application number:
**PCT/JP98/04532**

(87) International publication number:
**WO 99/17746 (15.04.1999 Gazette 1999/15)**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE**

(30) Priority: **07.10.1997 JP 27484297**

(71) Applicant: **Eisai Co., Ltd.**
**Tokyo 112-8088 (JP)**

(72) Inventors:
- **KATO, Yoshiteru**
  **Saitama 367-0043 (JP)**
- **SUZUKI, Toru**
  **Tokyo 202-0004 (JP)**
- **ABE, Shinobu**
  **Saitama 362-0042 (JP)**
- **TOKIZANE, Makoto**
  **Saitama 330-0038 (JP)**

(74) Representative:
**Türk - Gille - Hrabal - Struck**
**Patentanwälte - European Patent Attorneys,**
**Brucknerstrasse 20**
**40593 Düsseldorf (DE)**

## (54) PROCESS FOR PREPARING EMULSIFIED POWDER

(57) A process for preparing an emulsified powder by mixing an oil-soluble substance, a modified starch and, if desired, a vegetable gum with water to prepare an emulsion, followed by drying. As the obtained powder is reduced in degradation due to impact applied thereto during tabletting, it is reduced in the exudation of oil. The tablet prepared from this powder is easy to handle, meter and intake, so that it is utilized in the wide fields of food and drink, drugs, and the like.

EP 0 972 513 A1

## Description

### TECHNICAL FIELD

**[0001]** This invention relates to a process for the preparation of emulsified powders of an oil-soluble substance. The emulsified powders prepared according to the invention are suitable for tableting, because the cells encapsulating oil particles are hardly disintegrated by compressing impact, leading to less oil exudation.

### BACKGROUND ART

**[0002]** Emulsified powders containing oil-soluble substances such as edible fats have been prepared by emulsifying and dispersing oil-soluble substances in water using an emulsifying agent such as gum arabic, a filler such as dextrin or the like and then drying the emulsion thus obtained by a conventional drying means such as spray drying, drum drying, belt drying, freeze drying or the like. It has been also carried out to emulsify oil-soluble substances using as an emulsifying agent synthetic surfactants such as glycerol fatty acid esters, polyglycerol fatty acid esters, sucrose fatty acid esters and the like.

**[0003]** The emulsified powders prepared using gum arabic have a tough coated film and are relatively suited for tableting, but the emulsified particles are difficult to be finely divided. Further, because gum arabic in an amount of about two or three times that of the oil-soluble substance is required, the oil-soluble substance has a limited content.

**[0004]** Although synthetic surfactants are excellent in emulsifying property, a coated film is so weak that the emulsified cells may be disintegrated during the drying step and oil exudation is observed over the surface of powders at a higher rate, and the surfactants are not suited for pulverizing an oil-soluble substance.

**[0005]** As an alternative to the emulsified powders, there have been proposed mononuclear capsules by microcapsulation using gelatin, but they have the drawbacks that the surface thereof may be converted to a hardened film by formalin treatment or the like, so that there is a high possibility of disintegration in the coated film portion and said portion is disintegrated in the course of tableting.

**[0006]** As is explained above, when tablets or the like are to be prepared using the emulsified powders of the oil-soluble substance as prepared according to the prior art, oil exudation may be frequently brought about by compressing the emulsified powders having a higher content of the oil-soluble substance, thus the amount thereof to be added is limited. In the case of the emulsified powders having a lower content of the oil-soluble substance, a larger amount of the emulsified powders should be used, but the amount thereof to be added has its limit in view of the composition of a tablet. Therefore, tablets having a higher content of the oil-soluble substance are presently not obtainable. When a large amount of the oil-soluble substance is to be ingested in the form of tablets as health food, tablets having a higher content of the oil-soluble substance are desired. Under these circumstances, there have been eagerly expected emulsified powders of an oil-soluble substance which do not induce any oil exudation in the course of tableting.

### DISCLOSURE OF INVENTION

**[0007]** It is an object of the present invention to provide emulsified powders containing an oil-soluble substance, wherein the cells containing oil particles are stable against impact and oil exudation is not brought about in the course of tableting.

**[0008]** We have made earnest studies to solve the above problems, and as a result, have found that less disintegrative emulsified powders can be obtained by emulsifying a core substance of an oil-soluble substance such as edible fats or the like with a chemically modified starch and drying the resulting emulsified dispersion using a conventional drying means, upon which the present invention has been completed. Moreover, we have found that emulsified powders with a superior quality can be obtained by coating an oil-soluble substance with both a chemically modified starch having an excellent emulsifying property and a vegetable gum having an excellent coating property.

**[0009]** Accordingly, the invention relates to a process for the preparation of emulsified powders which comprises emulsifying an oil-soluble substance and a chemically modified starch in water and then drying the emulsion.

**[0010]** Also, the invention relates to a process for the preparation of emulsified powders which comprises emulsifying an oil-soluble substance, a chemically modified starch and a vegetable gum in water and then drying the emulsion.

**[0011]** The emulsified powders prepared according to the invention are an aggregate of a great number of particles (cells) in which a core substance of the oil-soluble substance is coated with the chemically modified starch or the like, and a particle diameter thereof is preferably 50-500 μ. The emulsified particles when emulsified in water have preferably a particle diameter of 2 μ or less.

**[0012]** The oil-soluble substance which may be used in the invention includes fat-soluble vitamins such as vitamin A, vitamin E, vitamin A acetate, vitamin E acetate and the like; unsaturated higher fatty acids such as DHA (docosahexaenoic acid), EPA (eicosapentaenoic acid) and the like; oil-soluble flavors such as orange oil, lemon oil, peppermint oil

and the like.

**[0013]** The chemically modified starch as used in the invention refers to an ester of a starch with an organic acid having an emulsifying activity, which is referred to as "Food starch-modified" in the Gazette of the United States, CFR (FDA) 172.89 (d), 1995. Examples of said organic acid may include succinic acid, acetic acid, adipic acid or an alkyl or alkenyl derivative thereof such as octenyl succinate. As the chemically modified starch is particularly preferred octenyl succinate starch, which is a half ester of a starch and octenyl succinate (See U.S. Patent No. 3,971,852), or a salt thereof, whose examples may include "EMULSTAR 30A" (trade name, manufactured by MATSUTANI KAGAKU KOGYO CO., LTD.), "CAPSULE" (trade name, manufactured by National Starch & Chemical Nippon NSC LTD.)

**[0014]** The vegetable gum which may be used in the invention includes gum arabic, xanthan gum, guar gum and the like, as well as pullulan, pectin and the like.

**[0015]** In practicing the present process, to a mixture of 150-200 parts (parts by weight, which will be similarly applied hereinafter), 1-90 parts of the chemically modified starch and, if desired, 1-50 parts of the vegetable gum was added 10-60 parts of the oil-soluble substance and then the mixture was stirred at a temperature of 10-60°C at a revolution number of 5000-15000 per minute for 5-20 minutes to prepare an emulsion of the oil-soluble substance. In order to reduce disintegration during tableting, it is desirable that an emulsified particle diameter may be preferably 2 μ or less. The emulsifier to be applied may be suitably a high-speed agitating emulsifier with a higher shear force such as "CLEARMIX" (trade name, manufactured by M TECHNIQUE) or a high pressure emulsifier such as a homogenizer, but it is not limited to said emulsifiers. The emulsion thus prepared may be dried as such by any suitable means such as spray drying, drum drying, belt drying, freeze drying or the like to prepare emulsified powders having excellent tableting performances. The emulsified powders obtained by the process of the invention have a good water-dispersion property and also a superior fluidizing property.

EXAMPLES

**[0016]** The present invention will be more specifically illustrated by way of the following Examples.

Example 1

**[0017]** In 150 g of water were dissolved 20 g of a chemically modified starch (manufactured by MATSUTANI KAGAKU KOGYO CO., LTD.; trade name of "EMULSTAR 30A"), 30 g of lactose and 20 g of gum arabic and the solution was sterilized by heating at 85-90°C for 15 minutes. This solution was cooled to 40°C or lower, 30 g of vitamin E was added and admixed and then emulsified by means of TK-HOMO-MIXER (manufactured by TOKUSHU KIKA KOGYO CO., LTD.). The emulsified particles were re-emulsified by means of "CLEARMIX" (trade name of an emulsifier manufactured by M TECHNIQUE) so as to provide finely divided particles. The emulsion thus prepared was spray-dried at an inlet temperature of 140°C and an exhaust temperature of 90°C using a spray drier (manufactured by OHKAWARA KAKOHKI CO., LTD.) to afford 90 g of emulsified powders of vitamin E (Product 1 of the invention).

Example 2

**[0018]** In 150 g of deaerated water were dissolved 30 g of a chemically modified starch (manufactured by National Starch & Chemical Nippon NSC LTD.; trade name of "CAPSULE"), 14 g of lactose and 25 g of gum arabic and the solution was sterilized by heating at 85-90°C for 15 minutes. This solution was cooled to 40°C or lower, 30 g of DHA oil and 1 g of vitamin E were added and admixed and then emulsified by means of TK-HOMO-MIXER. The emulsified particles were reemulsified by means of "CLEARMIX" (trade name of an emulsifier manufactured by M TECHNIQUE) so as to provide finely divided particles. The emulsion thus prepared was spray-dried at an inlet temperature of 140°C and an exhaust temperature of 90°C using a spray drier (manufactured by OHKAWARA KAKOHKI CO., LTD.) to afford 90 g of emulsified powders of DHA (Product 2 of the invention).

Example 3

**[0019]** Following the same procedure as described in Example 2 except that 30 g of peppermint oil was used instead of 30 g of the DHA oil, there was obtained 90 g of emulsified powders of peppermint oil.

Example 4

**[0020]** In 150 g of water were dissolved 20 g of the chemically modified starch as used in Example 1 and 50 g of dextrin (DE 10) and the solution was sterilized and then 30 g of vitamin E was added. Then, the same procedure as described in Example 1 was repeated to afford 90 g of emulsified powders of vitamin E (Product 4 of the invention).

Example 5

**[0021]** In 150 g of deaerated water were dissolved 30 g of the chemically modified starch as used in Example 2 and 39 g of dextrin (DE 10) and the solution was sterilized. Then, 30 g of DHA oil and 1 g of vitamin E were added. The same procedure as described in Example 1 was repeated to afford 90 g of emulsified powders of DHA (Product 5 of the invention).

Example 6

**[0022]** In 15 kg of purified water was dissolved 5 kg of a chemically modified starch (manufactured by MATSUTANI KAGAKU KOGYO CO., LTD.; "EMULSTAR 30A"). To the solution was added 5 kg of vitamin E acetate (manufactured by EISAI CO., LTD.) and then the mixture was emulsified by means of the TK-HOMO-MIXER and a pressure emulsifier. The emulsion was spray-dried at an inlet temperature of 160°C and an exhaust temperature of 80°C by means of a spray drier (manufactured by OHKAWARA KAKOHKI CO., LTD.) to prepare emulsified powders of vitamin E. To 990 g of the emulsified vitamin E powders thus prepared was added 10 g of hydrous silicon dioxide (manufactured by FUJI SILYSIA CHEMICAL LTD.; "SILYSIA 355") as a fluidizing agent and admixed to afford emulsified powders of vitamin E (Product 6 of the invention).

Reference Example 1

**[0023]** Following the same procedure as described in Example 4 except that an equal amount of gum arabic was used instead of the chemically modified starch, there was obtained 90 g of emulsified powders of vitamin E (Reference Product 1).

Reference Example 2

**[0024]** Following the same procedure as described in Example 5 except that an equal amount of gum arabic was used instead of the chemically modified starch, there was obtained 90 g of emulsified powders of DHA (Reference Product 2).

Comparative Example 1

**[0025]** Tablets were prepared by tableting the following formulations according to a conventional method. The tablets thus prepared were stored in polyethylene bags at 40°C for one week.

Table 1

| | Examples of formulations | | | | | |
|---|---|---|---|---|---|---|
| | No. 1 | No. 2 | No. 3 | No. 4 | No. 5 | No. 6 |
| Powder sugar | 93.0 | 93.0 | 93.0 | 93.0 | 93.9 | 93.0 |
| Sucrose fatty acid ester | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Powdered peppermint flavor | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Product 1 of the invention | 5.0 | - | - | - | - | - |
| Product 2 of the invention | - | 5.0 | - | - | - | - |
| Product 4 of the invention | - | - | 5.0 | - | - | - |
| Reference Product 1 | - | - | - | 5.0 | - | - |
| Product 5 of the invention | - | - | - | - | 5.0 | - |
| Reference Product 2 | - | - | - | - | - | 5.0 |
| Total (g) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |

**[0026]** Surface of the above tablets was microscopically observed, while one tablet (1.5 g) was dissolved in 30 g of water and the emulsified particles were microscopically observed. As a result, no oil exudation over the tablet surface

was observed in the formulations No. 1 and No. 2 in which Products 1 and 2 of the invention were incorporated respectively, and microscopic observation showed that the emulsified particles after being dispersed in water had a maximum size of around 3 μ and any disintegration of emulsified particles caused by compressing was not observed. In the formulation No. 3 or No. 5 in which Product 4 or 5 of the invention was incorporated, slight oil exudation over the surface of tablets was observed and partial disintegration of the emulsified particles was also observed, but each formulation was sufficiently applicable to practical use. On the other hand, in the formulation No. 4 or No. 6 in which Reference Product 1 or 2 was incorporated, partial oil exudation over the surface of tablets was observed and coalesced emulsified particles were observed by microscopic observation after being dispersed in water. After storing the tablets at 40°C for one week, organoleptic tests for their flavor were carried out by ten special panelists. It was judged that the formulations No. 1 and No. 2 in which Products 1 and 2 of the invention were respectively incorporated smelt of no deterioration odor during storage. On the other hand, it was judged by all the panelists that the formulation No. 4 or No. 6 in which Reference Product 1 or 2 was respectively incorporated smelt of noticeable deterioration odor during storage. When the formulations were evaluated prior to tableting according to the same method as described above, no significant difference was observed in the formulations No. 1 to No. 6. It may be considered from the above results that deterioration odor during storage could be caused by disintegration of emulsified particles in the course of tableting.

**[0027]** It is demonstrated from the foregoing that powders coated with the chemically modified starch and vegetable gums show less disintegration in tableting and excellent tableting property and thus are extremely useful.

INDUSTRIAL APPLICABILITY

**[0028]** According to the present invention, there is provided emulsified powders of an oil-soluble substance which show less disintegration of emulsified particles caused by compressing impact. The tableted product of the emulsified powders of the oil-soluble substance is easy in handling, weighing, ingesting and others and then can be utilized over a wide range of technical fields such as foods and drinks, medicaments or the like.

**Claims**

1. A process for the preparation of emulsified powders which comprises emulsifying an oil-soluble substance and a chemically modified starch in water and drying the emulsion thus formed.

2. A process for the preparation of emulsified powders which comprises emulsifying an oil-soluble substance, a chemically modified starch and a vegetable gum in water and drying the emulsion thus formed.

3. The process for the preparation of emulsified powders as claimed in claim 1 or 2 wherein said oil-soluble substance is an edible fat.

4. The process for the preparation of emulsified powders as claimed in claim 3 wherein said edible fat is a medicament or a health food.

5. The process for the preparation of emulsified powders as claimed in claim 3 wherein said edible fat is vitamin E or docosahexaenoic acid.

6. The process for the preparation of emulsified powders as claimed in claim 1 or 2 wherein said chemically modified starch is an ester of a starch with an alkenyl succinate.

7. The process for the preparation of emulsified powders as claimed in claim 6 wherein said alkenyl succinate is octenyl succinate.

8. The process for the preparation of emulsified powders as claimed in claim 6 wherein said chemically modified starch is octenyl succinate starch or sodium octenyl succinate starch.

9. The process for the preparation of emulsified powders as claimed in claim 2 wherein said vegetable gum is gum arabic.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/04532

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] A61K9/20, A61K47/36, A61K47/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] A61K9/20, A61K47/36, A61K47/46

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO, 90/7327, A1 (Taisho Pharmaceutical Co.,Ltd.), 12 July, 1990 (12. 07. 90) & EP, 401389, A | 1-9 |
| A | JP, 52-15812, A (Takeda Chemical Industries,Ltd.), 5 February, 1977 (05. 02. 77) & FR, 2318621, A & US, 4036948, A & GB, 1534066, A & DE, 2616078, A | 1-9 |
| A | JP, 3-258730, A (Asahi Chemical Industry Co.,Ltd.), 19 November, 1991 (19. 11. 91) (Family: none) | 1-9 |
| A | JP, 3-240723, A (Takeda Chemical Industries,Ltd.), 28 October, 1991 (28. 10. 91) (Family: none) | 1-9 |
| A | JP, 62-32844, A (Lotte Co., Ltd.), 12 February, 1987 (12. 02. 87) (Family: none) | 1-9 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 7 January, 1999 (07. 01. 99) | 19 January, 1999 (19. 01. 99) |
| Name and mailing address of the ISA/ Japanese Patent Office | Authorized officer |
| Facsimile No. | Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1992)